

Study Title: Cooling to Help Injured Lungs (CHILL) Phase IIB Randomized Control Trial of Therapeutic Hypothermia in Patients with ARDS

Document: Study Protocol Version 1.75

Updated: March 19, 2023

Changes made to version 1.74

1. Clarified the DNR exclusion to allow patients who are receiving full support EXCEPT chest compressions).
2. Clarified that the competing interventional trial exclusion is only for inpatient trials initiated during the current hospitalization.
3. Change the vasopressor exclusion from “requiring continuous administration of > 0.2 mcg/kg/min norepinephrine or equivalent dose of other vasopressors for at least 6 hr prior to randomization” “requiring to total vasopressor dose in norepinephrine equivalents exceeding $0.3 \mu\text{g/kg/min}$ within 2 hours of randomization”.
4. Change hypothermia exclusion from “hypothermia for ≥ 6 hrs (core temperature $< 35.5^{\circ}\text{C}$ while not receiving CRRT) within 24 h of randomization” to “hypothermia for ≥ 6 hrs (core temperature $< 35.5^{\circ}\text{C}$ while not receiving CRRT) on day of randomization.”
5. Added reminder for the hypotension, hypothermia, bleeding, and low platelet exclusions that the exclusion is time-dependent and patient should be followed until they exit the mechanical ventilation/ARDS window.
6. Neurocognitive (MOCA) testing has been removed.

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NCT No. NCT04545424

Document: Protocol Version 1.75

Updated: March 19, 2023

Funding source: U.S. Department of Defense (W81XWH2010432)

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1.0 Study Overview

1.1 Study Synopsis

The major objective of the proposed study is to test for the first time in a randomized control trial (RCT) the hypothesis that early treatment with therapeutic hypothermia (TH) along with neuromuscular blockade (NMB), to prevent compensatory shivering, will be beneficial for patients with Acute Respiratory Distress Syndrome (ARDS). The strategy of this Phase IIb RCT is to compare TH plus NMB vs. usual temperature management in patients with ARDS and $\text{PaO}_2/\text{FiO}_2$ ratio ($\text{P/F} \leq 200$). The hypothesis is supported empirically by the results of *in vitro* and animal studies and two small clinical studies. TH has a theoretical advantage over existing therapies because it may act through multiple mechanisms. If shivering is blocked by co-treatment with NMB, overall metabolism and the requirement for pulmonary gas exchange are reduced by ~10% for each 1°C decrease in core temperature¹. Thus, TH can confer a benefit similar to ECMO by reducing the requirement for mechanical ventilation, but with lower cost and risk than ECMO and with less requirement for specialized equipment and expertise. In addition to its potential to reduce mechanical ventilation-induced injury like other current therapies, hypothermia also restrains at least two signaling pathways that are directly involved in the pathogenesis of lung injury, Transient Receptor Potential Cation Channel Subfamily V Member 4 (TRPV4)² and p38 Mitogen-activated kinase (MAPK)³. The trial will be conducted in intensive care units (ICUs) at the University of Maryland Baltimore (Lead Center) and 13 additional centers (Johns Hopkins University, Thomas Jefferson, University of Pennsylvania, Temple University, Emory University, Cleveland Clinic, University of Illinois at Chicago, Loyola University – Chicago, Rush University, University of Wisconsin, Intermountain Health-Utah, Cooper Health, and Brooke Army Medical Center). Sites at Mayo Clinic Rochester, MN, University of Chicago, and Christiana Medical Center were closed for poor enrollment. To facilitate randomization within the inclusion window, we will use a 2-step enrollment/randomization protocol. The Christiana and University of Chicago sites were closed in year 2 and replaced by University of Wisconsin at Madison and Intermountain Health.

Patients will be eligible for enrollment when they have met all Berlin criteria for moderate to severe ARDS within the 72h inclusion window exclusive of P/F ratio. Enrolled patients will be randomized when P/F ratio (measured or imputed based on SpO_2) becomes ≤ 200 while on ≥ 8 cm H_2O PEEP. We plan to randomize a total 340 patients over the 3-year enrollment period to hypothermia (core temperature 34°-35°C for 48h) plus NMB or usual temperature management. The primary endpoint will be a composite of rank-transformed 28-day VFDs for those who survive to day 28 and worst rank scores assigned to those who die during the day 1-28 period according to day of death (lowest ranks assigned to those who die sooner). Secondary endpoints will include 28-day ICU-free days, oxygen saturation index (OSI), driving pressure, Sequential Organ Failure Assessment (SOFA) score, 60-day and 90-day survival and functional assessment, cognitive assessment at ICU and hospital discharge, and biomarkers of inflammation

and lung injury. Since the nature of the intervention precludes blinding, all treatment and clinical decision making related to study outcomes will be protocolized and compliance with study protocols will be monitored. This phase IIb RCT is designed to provide sufficiently definitive information about whether TH plus NMB reduces duration of mechanical ventilator dependency of patients with ARDS and will also inform a decision about whether to proceed with a Phase III clinical trial of TH to reduce mortality in ARDS and to direct its study design. Independent clinical monitoring will be provided by Navitas Clinical Research (NCR) (formerly KAI Research), Serious Adverse Event (SAE) monitoring and analysis will be provided by Medical Vigilance Solutions (MVS), and data management and randomization will be performed by the VA Cooperative Studies Program Coordinating Center (CSPCC) in Perry Point.

1.2 Study Aims and Objectives

We will objectively test our central hypothesis by conducting the multicenter randomized, controlled Cooling to Help Injured Lungs (CHILL) Phase IIb RCT of mild TH in patients with ARDS and $P/F \leq 200$ to address the following *specific aims*:

1. **Analyze the potential lung protective effect of mild TH (core temperature 34°-35°C for 48h) and NMB in patients with ARDS and $P/F \leq 200$ compared with controls receiving standard temperature management.** We expect the TH-treated group to have more 28-day VFDs (primary) and 28-day ICU-FDs, fewer deaths, and improved day-3 driving pressure and OSI than the controls.
2. **Evaluate the effects of TH on systemic inflammation and extrapulmonary organ dysfunction.** We expect the treated group to have reduced circulating levels of proinflammatory mediators and lower Sequential Organ Failure (SOFA) scores than controls.
3. **Analyze safety of TH in patients with ARDS.** We expect ARDS patients cooled to only 34°-35°C to exhibit few of the known complications of more extreme post-cardiac arrest TH (infections, hyperglycemia secondary to insulin resistance, electrolyte abnormalities, bradycardia, hypotension, and delayed recovery from NMB).

The proposed study will determine whether treating ARDS patients with TH and NMB will reduce duration of mechanical ventilation dependency. Although not planned as a survival study, we anticipate this study will provide sufficiently definitive information about the safety and benefit of TH plus NMB in patients with ARDS to inform a decision about whether to proceed with a Phase III clinical trial of TH to reduce mortality in ARDS and to direct its study design.

1.3 Background and Rationale

A substantial body of literature suggests that fever worsens, and hypothermia mitigates acute lung injury (ALI). Prior studies show that exposure to febrile-range hyperthermia (FRH) impairs endothelial barrier function, increases leukocyte transendothelial migration potential, and increases epithelial cytokine expression and apoptosis in cell culture, and worsens lung injury in animal models induced by LPS instillation, bacterial pneumonia, hyperoxia, and mechanical ventilation. In our reanalysis of core temperature and outcomes in the Improving Care of Acute Lung Injury Patients (ICAP) study database, 65% of ARDS patients had fever within the first 3

days of developing ARDS and the presence of fever reduced the likelihood of ventilator liberation within 24h by 33%. Hypothermia was lung-protective compared with normothermia in animal models of ALI induced by intratracheal LPS, paraquat, hemorrhagic shock, mechanical ventilation, pneumococcal pneumonia, and air embolism. The Villar and Slutsky non-randomized concurrently controlled trial of TH in patients with septic shock and ARDS also showed a modest increase in PaO₂/PAO₂ ratio (0.19±0.04 vs. 0.15±0.04) in the hypothermic group. A recent small retrospective review of cardiac arrest cases showed that treatment with a standard TH protocol (core temperature 32°-34°C) tended to improve respiratory mechanics. Studies from our laboratory and others suggest that signaling events that cause pulmonary vascular permeability, including MAPKs and the stretch-activated ion channel, TRPV4, are suppressed by clinically relevant hypothermia, providing potential mechanisms for lung-protective effects of hypothermia. These studies provide strong support for our hypothesis that TH will benefit patients with ARDS.

As a first step to analyzing the benefit of TH in ARDS, we completed a historically controlled open-label pilot study that addressed the feasibility of studying TH in ARDS patients receiving NMB. Our retrospective review of 58 patients with ARDS (P/F <150) receiving cisatracurium in the University of Maryland Medical Center (UMMC) Medical Intensive Care Unit (MICU) from 2012-15 showed that NMB alone did not cause hypothermia or prevent fever. The review identified continuous renal replacement therapy (CRRT) as a confounder that caused unintentional hypothermia during NMB, which the CHILL-pilot addresses in its temperature management protocols (see Interventions). Our open-label pilot study of TH in 8 consecutive NMB-treated ARDS (P/F <150) patients demonstrated feasibility of maintaining TH in this population. Target temperature was reached within 4hr and maintained for 92% of the 48h cooling period using Cincinnati Sub-Zero Blanketrol™ II cooling blankets (6 patients) and the Artic Sun™ system (2 patients). Cooling and rewarming were well tolerated without SAEs. Comparison with historical controls, who had similar ARDS severity and received NMB without cooling, showed that median (interquartile range/IQR) core temperature was 2.3°C lower in the cooled patients than controls (34.4 (34-34.8)°C vs. 36.65 (36-37.3)°C; p<0.0001). When compared to historical controls, the cooled patients showed trends toward reduced hospital mortality (25% vs. 53.4%, p=0.26), higher 28-day VFDs (9 (0-21.5) vs. 0 (0-12), p=0.16), and higher day 3 P/F ratio (255 (160-270) vs. 171 (120-214); p = 0.024). Since all patients were treated using ARDSNet ventilator and fluid management protocols and NMB, these results suggest TH during the first 72h of ARDS may confer benefit that is additive with current therapy.

1.4 Abbreviations and Acronyms

ALI: Acute lung injury

ARDS: Acute respiratory distress syndrome

CCC: Clinical Coordinating Center

CEC: CHILL Executive Committee

CHILL: Cooling to Help Injured Lungs

CRF: Case Report Forms

CRRT: Continuous Renal Replacement Therapy
CSPCC: Cooperative Studies Program Coordinating Center (in Perry Point, MD)
CVC: Central Venous Catheter
CVP: Central Venous Pressure
DCC: Data Coordinating Center
DoD: Department of Defense
DSMB: Data Safety Monitoring Board
DSMP: Data Safety Monitoring Plan
ECMO: Extracorporeal Membrane Oxygenation
ETT: Endotracheal Tube
F_IO₂: Fractional Index of Inhaled Oxygen
FRH: Febrile-range Hyperthermia
HRPO: Human Research Protection Office
HSCTI: Human Subject Clinical Trial Information
ICAM: intercellular adhesion molecule
I:E: Inspiration: Expiration
IL: Interleukin
LAR: Legally Authorized Representative
MICU: Medical Intensive Care Unit
MOCA: Montreal Cognitive Assessment
MVS: Medical Vigilance Solutions
MMP: Matrix Metalloproteinase
NCR: Navitas Clinical Research
NMB: Neuromuscular Blockade
OSA: Obstructive Sleep Apnea
OSI: Oxygen Saturation Index
PAC: Pulmonary Artery Catheter
P_aO₂: Partial Pressure of Oxygen in Arterial Blood
PEEP: Positive End-Expiratory Pressure
P/F: P_aO₂/F_IO₂:Ratio
PICC: peripherally inserted central catheter
P_{plat}: Airway plateau pressure
RAGE: Receptor for Advanced Glycation Products
SAE: Serious adverse event
SOFA: Sequential organ failure assessment
SP-D: surfactant protein-D
sTNFRI: soluble TNF receptor-1
TH: Therapeutic hypothermia
TNF α : Tumor Necrosis Factor- α

UMMC: University of Maryland Medical Center

VFDs: Ventilator-free days

2.0 Data Safety Monitoring Plan (DSMP)

2.1 DSMB composition

A Data Safety Monitoring Board (DSMB) has been appointed by the CHILL Executive Committee (CEC) with DoD approval. The DSMB is chaired by an intensivist with experience in ARDS and clinical trials (Dr. James Shelhamer), a biostatistician (Dr. Wendy Mack), an expert in targeted temperature management (Dr. Brian O'Neill), and two additional intensivists with experience in clinical trials in ARDS (Drs. Kathleen Liu and Lorraine Ware).

2.2 DSMP Procedures

The Data Coordinating Center (DCC) is responsible for managing Data Safety Monitoring, including preparing reports for bi-annual review by the DSMB. Assessment of clinically significant adverse events will be performed throughout the ICU hospitalization. The DSMB, which reports directly to the IRBs and DoD HRPO and oversees study subject safety and protection, will review the study data provided by the DCC and the Independent Research Monitor. The CHILL adverse event reporting protocol was developed to account for the following aspects of the CHILL study: (1) the expected mortality for the study population is ~40%; (2) the nature of the study intervention precludes blinding; (3) the study intervention, TH+NMB, for 48 hrs followed by slow re-warming, is self-limited with previously delineated potential clinical risks.

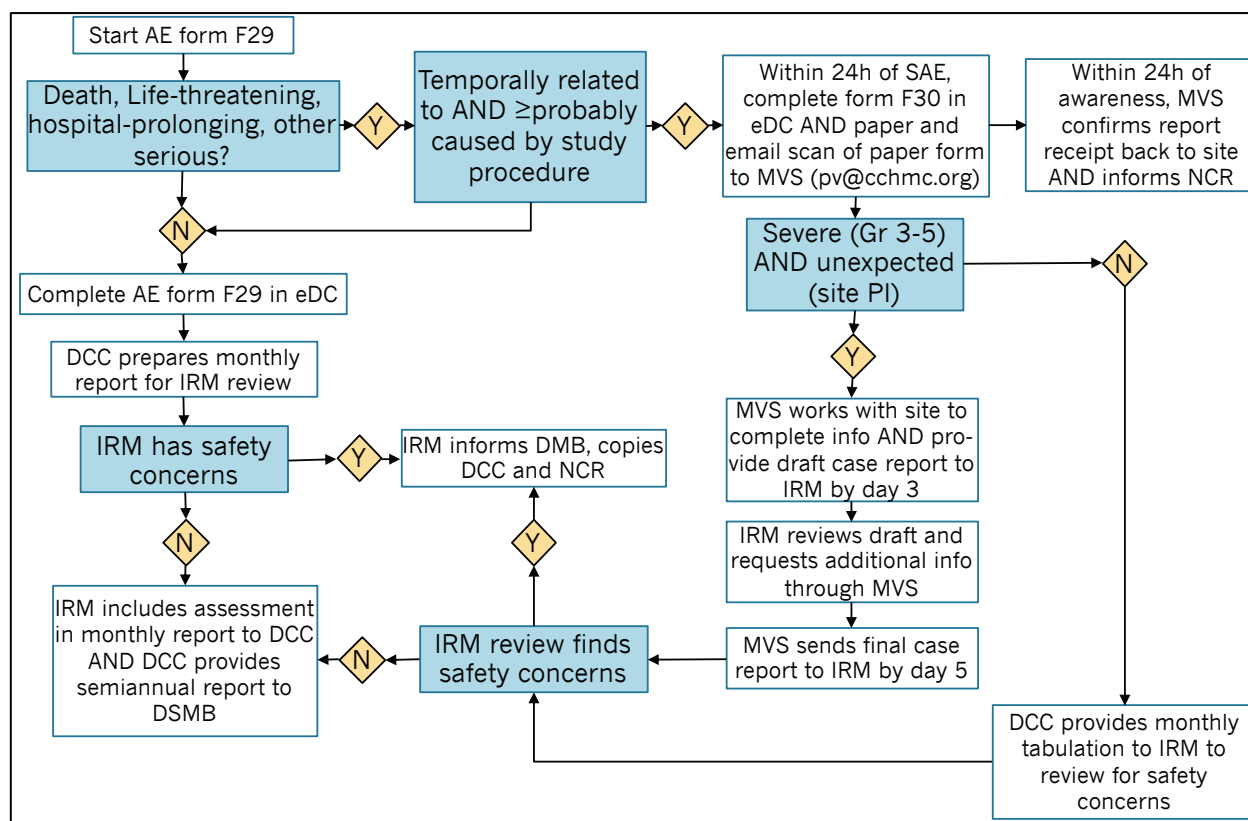
1. All Adverse Events (AEs) will be recorded on the Adverse Event Recording form (F29) in the eDC and will be tabulated by the DCC (see figure 3).
2. Any deaths or life-threatening events temporally related with study procedures, including cooling and rewarming, will be recorded on the Serious Adverse Event form (F30) and reported by site personnel within 24 hr to the adverse event monitoring group engaged by NCR through MVS. Site personnel will fill out the paper form and send a pdf of the form without patient identifiers other than the study ID number) to MVS as an email attachment attachment to pv@cchmc.org. MVS will contact the site and ensure that all patient data required for analysis of the SAE, including the site PI's assessment of severity and study-relatedness, are collected. If the AE is severe and related to the study, MVS will notify the CHILL Independent Research Monitor (Dr. Michael Mazzeffi). If the AE is felt to be unrelated, the event will be added to the monthly report prepared for Dr. Mazzeffi. If Dr. Mazzeffi requires additional information related to the SAE, he will send a request to MVS rather than contact the site directly. The information regarding the AE/SAE will be entered into the eDC **and signed by the PI. Should Dr. Mazzeffi not be available, Dr. Shelhamer will temporarily assume his responsibilities.**
3. The independent research monitor will monitor for patterns of SAEs that suggest potential problems with subject safety and report these to the DSMB Chairman, Dr. Shelhamer. Other-

wise the SAEs will be included in the biannual DSMB report. The DSMB will evaluate the concerning data received from the independent research monitor and if they concur about safety issues, they will notify the CEC, the central IRB, and DoD HRPO.

4. Pre-specified minor abnormalities will be tabulated as adverse events (distinct from SAEs) in the semi-annual reports to the DSMB.

5. The study leadership will act promptly on any safety concerns or recommendations articulated by the DSMB.

Figure 3: SAE reporting flow diagram.



The site ID numbers are:

- | | |
|----|------------------------------------|
| 1 | University of Maryland |
| 2 | Brooke Army Medical Center |
| 3 | Christiana Medical Center - closed |
| 4 | Cleveland Clinic |
| 5 | Emory University |
| 6 | Loyola-Chicago |
| 7 | John Hopkins University |
| 8 | Thomas Jefferson University |
| 9 | Mayo Clinic Rochester, MN - closed |
| 10 | University of Pennsylvania |
| 11 | Rush University |
| 12 | Temple University |
| 13 | University of Chicago - closed |
| 14 | University of Illinois Chicago |
| 15 | University of Wisconsin at Madison |
| 16 | Intermountain Health |
| 17 | Cooper Health |

Any screened patient identified as meeting any of Study exclusion criteria (see below) will be excluded from further study activities. Women of child-bearing potential who otherwise meet enrollment/randomization criteria will be offered a pregnancy test prior to enrolling.

4.0 Enrollment and Randomization*

4.1 Study Inclusion Criteria

1. men and women
2. any race/ethnicity
3. 18 years, 0 days - 75 years, 364 days of age
4. endotracheal tube or tracheostomy in place and mechanically ventilated for ≤ 7 days;
5. admitted to a participating ICU
6. radiologic evidence of bilateral pulmonary infiltrates
7. P/F ratio ≤ 200 with PEEP ≥ 8 cm H₂O; If ABG values are not available, the P/F ratio may be inferred from SpO₂ values based on Table 3 from Brown et al ⁴ as long as following conditions are met:
 - a. SpO₂ values are 80-96%
 - b. SpO₂ is measured ≥ 10 min after any change in F_IO₂
 - c. PEEP is ≥ 8 cm H₂O
 - d. the pulse oximeter waveform tracing is adequate
 - e. the qualifying inferred P/F ratio is confirmed 1-6 hrs after the initial determination.

eTable 2: Imputed PF ratio (cells) for combinations of SpO₂ (rows) and FiO₂ (columns)

	0.30	0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95	1.00
80%	148	127	111	98	89	81	74	68	63	59	55	52	49	47	44
81%	151	129	113	101	91	82	76	70	65	60	57	53	50	48	45
82%	155	132	116	103	93	84	77	71	66	62	58	55	52	49	46
83%	158	136	119	106	95	86	79	73	68	63	59	56	53	50	47
84%	162	139	122	108	97	89	81	75	70	65	61	57	54	51	49
85%	167	143	125	111	100	91	83	77	71	67	63	59	56	53	50
86%	171	147	129	114	103	94	86	79	73	69	64	61	57	54	51
87%	177	151	132	118	106	96	88	81	76	71	66	62	59	56	53
88%	182	156	137	121	109	99	91	84	78	73	68	64	61	58	55
89%	189	162	141	126	113	103	94	87	81	75	71	67	63	60	57
90%	196	168	147	130	117	107	98	90	84	78	73	69	65	62	59
91%	203	174	153	136	122	111	102	94	87	81	76	72	68	64	61
92%	213	182	159	142	128	116	106	98	91	85	80	75	71	67	64
93%	223	191	168	149	134	122	112	103	96	89	84	79	74	71	67
94%	236	202	177	157	142	129	118	109	101	94	89	83	79	75	71
95%	252	216	189	168	151	138	126	116	108	101	95	89	84	80	76
96%	273	234	205	182	164	149	136	126	117	109	102	96	91	86	82

Conditions required to use inferred P/F ratio include: (a) SpO₂ values 80-96%, (b) SpO₂ measured ≥10 min after FiO₂ change, (c) PEEP ≥ 8 cm H₂O, (d) adequate pulse oximeter wave form, and (e) qualifying inferred P/F ratio is confirmed 1-6 hrs after the initial determination.

-
8. For patients on APRV, the PEEP value will be calculated from the set parameters and measured Mean Airway Pressure (MAP) based on the formula:

$$MAP = \frac{T_{HIGH} \times P_{HIGH} + T_{LOW} \times PEEP}{T_{HIGH} + T_{LOW}}$$

and rearranging to yield:

$$PEEP = \frac{MAP \times (T_{HIGH} + T_{LOW}) - T_{HIGH} \times P_{HIGH}}{T_{LOW}}$$

9. Patient is able to give consent or a Legally Authorized Representative (LAR) is available to provide consent.
10. Criteria 6 and 7 must be met within 72h of enrollment and randomization, not be fully explained by hydrostatic pulmonary edema. Criterion 6 must have occurred within 7 days of exposure to a condition associated with ARDS, including COVID-19 (this is not restricted to initial exposure and can be within 7 days of continuous exposure to a risk factor).

*Patients may be enrolled and decision about randomization delayed if all criteria exclusive of P/F ratio ≤ 200 are met and then randomized if and when the P/F ratio ≤ 200 (as long as this occurs within the 72h ARDS window and 7-day mechanical ventilation window). If and when the P/F ratio criterion is achieved within the inclusion windows, the patient is eligible for randomization even if the P/F ratio subsequently exceeds 200 prior to randomization (e.g. while waiting for consent). The 72h ARDS inclusion window begins when the patient meets the criteria for bilateral pulmonary infiltrates and P/F ratio ≤ 200 while supported with one of the following modes of assisted breathing: (1) intubated or with a tracheostomy or with non-invasive pressure support ventilation with well-fit mask and PEEP ≥ 8 cm H₂O; or (2) P/F ratio ≤ 184 on high flow nasal cannula with flow rate ≥ 40 L/min and FIO₂ ≥ 0.65 and well-fit cannula.

4.2 Study Exclusion Criteria

1. Missed moderate to severe ARDS window (>72hrs)
2. Missed NMB window (continuous NMB for at least 48 hrs prior to randomization: If is interrupted or discontinued before the patient exits the MV and ARDS windows, they are eligible for enrollment.)
3. Missed mechanical ventilation window (>7 days)
4. Refractory hypotension (requiring continuous administration of > 0.3 mcg/kg/min norepinephrine or equivalent dose of other vasopressors within 2 hrs of randomization).
Note – this exclusion is time-dependent; if hypotension resolves before the patient exits the MV and ARDS windows, they are eligible for enrollment.
5. Spontaneous hypothermia for ≥ 6 hrs (core temperature $< 35.5^{\circ}\text{C}$ while not receiving CRRT) on the day of randomization. Note – this exclusion is time-dependent; if hypotension resolves before the patient exits the MV and ARDS windows, they are eligible for enrollment.
6. Significant, active bleeding ($> 3\text{u}$ blood products and/or surgical/Interventional Radiology intervention) on day of randomization. Note – this exclusion is time-dependent; if bleeding resolves before the patient exits the MV and ARDS windows, they are eligible for enrollment.
7. Platelets $< 10\text{K}/\text{mm}^3$ (uncorrected) on day of randomization. Note – this exclusion is time-dependent; if severe thrombocytopenia resolves before the patient exits the MV and ARDS windows, they are eligible for enrollment.
8. Active hematologic malignancy
9. Skin process that precludes cooling device
10. Moribund, not likely to survive 72h
11. Pre-morbid condition makes it unlikely that patient will survive 28 days
12. Do Not Resuscitate status (except for patients who are receiving full support except chest compressions)
13. Not likely to remain intubated for $\geq 48\text{h}$
14. Physician of record unwilling to participate
15. Severe underlying lung disease
 - a. Needs home O₂ $\geq 2\text{LPM}$ or $\geq 28\%$

- b. On home noninvasive ventilation (except for treating OSA)
- c. Prior lung transplantation
- 16. BMI >50 kg/m²
- 17. Known NYHA class IV heart disease
- 18. Pregnant
- 19. Acute Coronary Syndrome past 30 days (MI, unstable angina)
- 20. Cardiac arrest within 30 days of enrollment
- 21. Received ECMO during current hospitalization
- 22. Burns over >20% of the body surface
- 23. Severe chronic liver disease (Child-Pugh score 12-15)
- 24. Previously enrolled in CHILL study
- 25. Simultaneous enrollment in another inpatient interventional trial initiated during the current hospitalization

4.3 Screening and Enrollment Procedures

All patients in participating CHILL units who are 18-75 years old and intubated or have a tracheostomy in place and have been receiving mechanical ventilation for ≤7 days screened for potential exclusion criteria using forms F01 and F02. To reduce the number of patients who are screened and not enrolled, we will not screen patients who are known to have had a cardiac arrest in the last 30 days, have an active DNR order, a history of lung transplant, are known to be pregnant, are likely to be weaned from the ventilator within 48h (based on the assessment of CHILL personnel), or for whom withdrawal of care/end of life discussions are planned. It is possible that one of these conditions may not be identified until after the patient has already been screened and a study ID generated (e.g. a pregnancy test is positive or patient made DNR after screening). In this case the appropriate exclusion criteria will be entered on the Eligibility Summary Form F02 and screening failure indicated. For the conditions that preclude screening that are reversible (e.g. DNR status, estimate of likelihood of weaning from the ventilator within 48h, or pregnancy status), the patients will be tracked and subsequently screened and evaluated for enrollment/randomization if appropriate. All patients who are screened will be sequentially assigned an 8-9-character study ID from a list prepared for each site and printed on the screening log. Patient identifying information will be recorded on the screening log. The screening log and a back-up copy will remain at the clinical site in two distinct locations. If the patient has any of the disqualifying exclusion criteria listed on the Eligibility form (F02), they will be excluded. Otherwise, they will be evaluated for enrollment and randomization criteria (forms F03-F06) and enrolled or followed until they meet enrollment criteria, develop an exclusion criterion, or exit the inclusion window. The lowest values for P/F ratio for each day of mechanical ventilation (up to 7 days) will be recorded on the P/F ratio form (F06). If the patient has been transferred from another hospital, P/F ratio from the transferring hospital will be recorded. Female patients with reproductive potential who meet all other criteria for enrollment will be tested for pregnancy if not already done during the hospitalization and excluded if pregnant. Demographic information and final enrollment status, and the reason for exclusion (if ap-

plicable) will be entered into the Screening log, password-protected, and kept until 3 years following study completion. To facilitate informed consent, we allow enrollment if patients meet all criteria for moderate to severe ARDS except the P/F ratio ≤ 200 and randomize if and when a P/F ratio is measured or imputed (from SpO₂). We anticipate that all consent will be obtained from the patients' LAR. If consent is obtained, the patient will be enrolled and the "Yes" box on the enrollment form (F05) will be checked. If the patient meets enrollment criteria but consent cannot be obtained, the patient will be excluded from the study. If patients meet criteria for enrollment and randomization, they will be enrolled, essential baseline data and the baseline research blood sample will be collected, and the patient will be randomized. Otherwise, they will be monitored until they meet the P/F ratio criterion or exit the mechanical ventilation inclusion window.

4.4 Informed Consent Process

Patients found on screening to qualify for enrollment and whose ICU provider agrees will be offered participation in CHILL. Because eligible patients will be seriously ill, on high levels of mechanical ventilation, and receiving sedation and possibly NMB, informed consent will be obtained from the patient's LAR by the CHILL site personnel. The information provided in the consent will cover the elements listed in the 21 CFR Part 50.25 and be approved by the UMB IRB. This includes the investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks, discomforts, and benefits, and potential alternatives including not participating and right to withdraw without penalty. Study staff personnel will offer to answer any questions. Consent will be documented by LAR signature on the currently IRB-approved consent form LAR. No study procedure will be done prior to obtaining signed informed consent. The central IRB allows for remote consent. Sites may obtain consent from the LAR remotely within the guidelines of their local IRB using the eConsent platform supported by their institution. Once patients regain decision making capacity as assessed using an IRB-approved Capacity Assessment tool, informed consent for continuing participation in CHILL will be obtained a Clinical Research Team member.

If patients or their LAR decide to rescind consent, study personnel will determine which study procedures, including analysis of data collected and additional data collection they will permit. This information will be recorded on the Study Withdrawal form (F89).

Patients or their LAR may withdraw specimens from CHILL as part of their right to withdraw from CHILL. Upon receipt of a request for reduction in participation in CHILL, clinical site staff will discuss with the patient or LAR the extent of the request -- e.g., end of in-person contact but telephone calls allowed, end of in-person contact and telephone calls but review of medical record allowed, end of specimen collection but use of specimens already collected allowed, withdrawal of specimens already collected -- and document the request and its extent in writing to provide the information to the study leadership for proper data collection and specimen management.

4.5 Safeguards for Vulnerable Population

We anticipate that most potential CHILL subjects will be cognitively impaired, at least temporarily, as a result of meeting the inclusion criteria for this study for study entry. In these cases, informed consent will be obtained from a LAR and subjects will be re-consented once they regain decision-making capacity. Such subjects will be considered vulnerable patients. Based on our underlying hypothesis, the subjects randomized to the TH + NMB arm may derive benefit from the experimental therapy. Subjects in both arms will derive benefit from the additional monitoring by the research team and the use of protocolized evidence-based care as a consequence of participating in the CHILL trial. If patients are not re-consented during their hospitalization and regain decision-making capacity after hospital discharge, they will be informed about their trial participation and asked to provide information about their functional status when be contacted for the 60-day phone contact. Agreement to provide such information will be accepted as implied consent for CHILL participation. If the patient regains capacity between the 60-day and 90-day follow-up, they will be asked to provide functional information at the 60 and 90-day contacts.

4.6 Retention Strategies

We anticipate that most participating subjects will remain hospitalized, likely in the ICU, through study day 7 and accessible to study personnel. Patients will be seen daily by study personnel through the first 7 days for data collection, protocol adherence, and collection of research samples. Beyond study day 7 patient status will be monitored by examining the medical record and, as needed, bedside visit. Study personnel will complete CRFs for ICU discharge, study day 28 status, and hospital discharge. The hospital discharge CRF will contain patient disposition and contact numbers, including the patient's LAR to facilitate 60-day and 90-day follow-up.

4.7 Outreach to Minorities and Women

The composite CHILL patient population is well-represented in minorities and women (Table 1). There are no exclusions based on race, ethnicity, or gender. Pregnancy will be an exclusion because there are no data to ensure safety of mild hypothermia for the fetus. Pregnancy testing will be performed in all women of child-bearing age prior to randomization.

4.8 Engagement of Clinical Community to Encourage Recruitment

Presentations about CHILL will be given as Grand Rounds at each clinical site and their referring hospitals as well as to institutional critical care committees. The site PI and coordinator will educate staff and phy-

Table 1. Site Information

Site Name	Site PI	ICU beds			ARDS (P/F<200) pts /yr	Percent AA ¹ HP ²		Planned enrollment (total 3 yr)
		Med.	Surg	Trauma				
Brooke Army MC	Whitney Warren Robert Walter	18		17 ³	250	15	20	15
Christiana	Matthew Barrett	22	22		100	35	10	25
Cleveland Clinic	Abhijit Duggal Rachel Scheraga	64	31		250	44	4	25
Emory	Jonathan Sevransky	17	23		100	20	10	25
Loyola-Chicago	Majid Afshar	35	30 ³		498	30	17	25
Hopkins	Robert Stephens	24			150	50	20	25
Jefferson	Michael Baram	25		17	200	20	70	25
Mayo	Lioudmila Karnatovskaia Richard Oekler	52	20		50	4.8	3.9	25
Penn	Jason Christie	36	24		65	34	2	25
Rush	Jared Greenberg	28	28		120	40	25	25
Temple	Gerard Criner Nathaniel Marchetti	28	20 ³		85	25	36	25
U Chicago	Bhakti Patel	24			30	60	10	25
UIC	Sunit Singla	19			30	30	50	25
U Maryland	Carl Shanholtz Ron Tesoriero	29	38	24	100	44	9	25

¹% African American

²% Hispanic

³Combined surgical/trauma beds

sicians for all participating ICUs about the CHILL trial. Signs with information about the CHILL trial including inclusion and exclusion criteria and easy contact information will be prominently displayed in all participating ICUs.

4.9 Randomization

Only patients who meet all the inclusion criteria, have none of the exclusion criteria, have a signed Informed Consent Form by themselves or their LAR, and have had the required pre-randomization BASELINE data and the BASELINE research blood sample secured (Forms F01, F06, F07, F12b, F17b, and F18) will be randomized.

The COVID-19 pandemic has resulted in a preponderance of ARDS patients infected with COVID-19 now. Although there are reasons to believe that the pathophysiology of organ injury, including ARDS, may be different in COVID-19 patients compared with other ARDS patients, we acknowledge that ARDS is a syndrome with diverse precipitating factors including COVID-19. Therefore, we will include patients with ARDS occurring in the setting of COVID-19 infection. Note that enrolling COVID-19 patients is not mandatory.

COVID-19 positive and negative patients will be combined for randomization purposes. A separate randomization schedule will be prepared for each site. Randomization will be performed within each site to receive TH or Usual Temperature Management using a 1:1 assignment ratio. Assignment of the subject to TH or Usual Temperature Management will be made by the web-based CSPCC randomization service.

4.9.1 Randomization Procedures

Select individuals with authorization to enter data will be authorized to randomize screened patients whose baseline data are complete and who are eligible for CHILL on the web-based randomization module accessed through the CHILL eDC system and managed by CSPCC. Patients with moderate to severe ARDS for ≤ 72 hr based on the Berlin criteria ⁵ will be enrolled and randomized. As mentioned earlier, patients without ABG data may be enrolled using a P/F ratio inferred from SpO₂ data as described by Brown et al. ⁴ and used in the ROSE trial ⁶. To facilitate randomization within the inclusion window, patients who meet all Berlin criteria but have not yet met the P/F ≤ 200 criterion may be consented, enrolled, and followed until P/F ratio becomes ≤ 200 or they exit the 72 hr ARDS window. Just prior to randomization, essential baseline data will be collected, a research blood sample will be drawn, an esophageal temperature probe will be placed if no other acceptable core temperature probe is present, and patients will be randomized to TH/NMB or usual temperature management. The web-based randomization system provided by the CSPCC Data Management and Randomization Core operates 24 hr/day and seven days per week (with Medidata back up in case of system failure). A pre-randomization checklist (Form F07) includes questions about meeting enrolment/randomization criteria, having consent, having the essential baseline data, including data required for calculating a SOFA and APACHE II score for the 24 hrs preceding randomization and a comprehensive metabolic panel (CMP) and complete blood count (CBC) within 24 hrs of randomization, and confirming that the baseline research blood sample was collected. The random allocation issued by this

system will be in the form of assignment to either the TH/NMB or usual temperature management arm. Each randomization is documented for time of issue on the computer system and under whose user ID authority the allocation is issued (i.e. who logged in for the randomization). APACHE II will be calculated from data obtained within 24 hrs of admission to the ICU. The SOFA score ⁷, driving pressure, P/F ratio, oxygenation index, and OSI will be calculated from baseline data obtained prior to randomization to assess comparability of disease acuity between groups.

Essential baseline data (required prior to randomization) includes Forms F01, F06, F07, F12b, F17b, and F18:

- Airway status (ETT/trach)
- Sex/age
- Height and ideal body weight
- Vital signs at time of randomization
- Vasopressors at time of randomization
- Body temperature and site of measurement at time of randomization
- Baseline ventilator settings
- Measured respiratory parameter at time of randomization
- Information about NMB at time of randomization (not receiving NMB or receiving for <48h)
- Proning status
- Qualifying P/F ratio (including associated PEEP and F_iO₂).

Additional baseline data (may be collected after randomization) includes forms F10, F11, F13, F14, F15, F19, F20, F21, and F22):

- Hospital admission date
- ICU admission date
- Type of ICU
- Where was patient admitted from?
- Pre-admission independence
- Actual body weight (calculated BMI)
- Smoking status info
- Surgery within last week (and type)
- Chronic health info and additional past medical history info
- Pre-hospital function status (
- Trach placed ≤ or > 30 days
- Data for APACHE II score calculation
- Inhaled pulmonary vasodilator/steroids at randomization
- For patients receiving continuous infusion NMB, time/date initiated
- On dialysis (Y/N)? type (peritoneal, iHD, CRRT)
- Data for SOFA score calculation
- Additional information about proning status
- Additional info on research blood processing and storage

5.0 Study Procedures

Both Arms undergo the same standard of Care procedures listed below.

5.1 Vital signs data collection

Heart rate, Blood Pressure, Respiratory rate, Pulse oximetry, Core temperature (esophageal or rectal, temperature sensing bladder catheters, central venous catheter, or pulmonary artery catheters, if present). All vital signs will be measured by standard of care and recorded as per study data collection requirements.

5.2 Ventilatory and respiratory parameters data collection

Ventilatory and respiratory parameters (Peak Airway Pressure (P_{peak}), Airway Plateau Pressure (P_{plat}), Positive End Expiratory Pressure (PEEP), and Mean Airway Pressure ($\overline{P_{\text{aw}}}$) will be obtained from the standard of care mechanical ventilation record collected as close as possible to 0800. Driving Pressure is calculated as the difference between airway plateau pressure and end-expiratory pressure ($P_{\text{plat}} - \text{PEEP}$) during a breath without spontaneous ventilator effort. Oxygen saturation index (OSI) is calculated as the product of mean airway pressure, fraction of inspired oxygen, and 100, divided by pulse oxygen saturation ($\overline{P_{\text{aw}}} \times \text{FIO}_2 \times 100 / \text{SpO}_2$) as long as the lowest SpO_2 measurement for the day was $< 97\%$.

5.3 Blood Laboratory values data collection

Hematology (WBC, Hgb, Hct, Platelets), Chemistry (Potassium, Bicarbonate, BUN, Creatinine, Glucose, Magnesium, Phosphate, Albumin, Bilirubin AST/ALT results measured by standard of care and recorded as per study data collection requirements. If the afternoon/evening basic metabolic panel, phosphate, and magnesium, which required on study day 1-3 are not required as part of standard care, they will be performed as a research laboratory test.

5.4 Fluid management data collection

Fluid management of ARDS patients enrolled in the CHILL Study, excluding patients in shock, will follow clinical guidelines of conservative approach to fluid management (see Table 1).

This conservative fluid management approach represents a simplification of the algorithm utilized in the ARDS Network FACTT study⁸. If not already being utilized, this conservative fluid management approach must be initiated within 4 hrs of randomization and continued until the subject has reached unassisted breathing (UAB) or study day 7, whichever occurs first.

1. Initial assessment and optimization of volume status: Assess for hypovolemia with bedside ultrasound if available (e.g. IVC collapsibility) and/or fluid responsiveness with passive leg raise (PLR); if hypovolemic resuscitate with fluid bolus; suggest starting with 10 mL/kg crystalloid rounded to nearest 250 mL and repeat until euvolemic. Defer diuresis for 12 hrs.
2. Recommend discontinuing maintenance fluids.
3. Continue medications and nutrition.
4. Manage electrolytes and blood products per usual practice.
5. For shock, use any combination of fluid boluses and vasopressor(s) to achieve mean arterial pressure $\geq 60\text{mm Hg}$ as fast as possible.

- Consider assessing for hypovolemia with bedside ultrasound (e.g. IVC collapsibility) and/or fluid responsiveness with passive leg raise (PLR) before bolusing fluid
 - Recommended fluid bolus = 15mL/kg crystalloid rounded to nearest 250 mL or 1 unit packed red cells or 25g albumin
 - Wean vasopressors as quickly as tolerated beginning approximately 4 hr after blood pressure has stabilized.
6. Withhold diuretic therapy in renal failure and until 12 hr after last fluid bolus or vasopressor use.
- Renal failure defined as dialysis dependence, oliguria with serum creatinine > 3mg/dL, or oliguria with serum creatinine 0–3 with urinary indices indicative of acute kidney injury).

Table 1: Guidelines for Fluid Management

CVP ^a	PAOP (optional)	MAP ≥ 60 mm Hg AND off vasopressors for ≥ 12h	
		Average urine output < 0.5 ml/kg/hr	Average urine output ≥ 0.5 ml/kg/hr
>8 ^b	> 12 ^b	Furosemide ^e Reassess in 1h	Furosemide ^e Reassess in 4h
4-8 ^c	8-12 ^c	Give fluid bolus Reassess in 1h	No intervention Reassess in 4h
< 4 ^d	< 8 ^d		

^aIf no central venous catheter (CVC), peripherally inserted central catheter (PICC), or pulmonary artery catheter (PAC, Swan-Ganz catheter), consider assessing volume status with ultrasound of IVC or NT-proBNP. If these assessments are normal, or not available, treat as euvolemic (CVP 4-8 or PAOP 8-12).

^bIf no CVC, PICC, or PAC present, can substitute distended IVC on bedside ultrasound or elevated NT-proBNP (adjusted for age)

^cIf no CVC, PICC, or PAC present, can substitute normal caliber IVC (neither distended nor collapsible) on bedside ultrasound or normal NT-proBNP (adjusted for age). If these assessments are unavailable, consider this euvolemic.

^dIf no CVC, PICC, or PAC present, can substitute collapsible IVC on bedside ultrasound

^eRecommended Furosemide dosing = begin with 20 mg bolus or 3 mg / hr infusion or last known effective dose. Double each subsequent dose until goal achieved (oliguria reversal or intravascular pressure target) or maximum infusion rate of 24 mg / hr or 160 mg bolus reached. Do not exceed 620 mg/day. Also, if patient has heart failure, consider treatment with dobutamine.

Fluid intake and output (I/O) will be obtained from EMR and recorded per study data collection requirements. I/Os will be computed every 24 hrs for the period starting at 0800 on the preceding day and ending at 0759 on the current study day.

5.5 Ventilator Management

To accommodate the different brands and models of mechanical ventilators used in CHILL sites, we have grouped the modes into five categories, volume-targeted, pressure-targeted, Airway Pressure Release Ventilation (APRV), Spontaneous, and Auto modes. Table 2 summarizes classification of ventilatory modes used in mechanical ventilators from five manufacturers.

Table 2: Classification of Mechanical Ventilator Modes

	Maquet Servo	Puritan Bennett	Hamilton	Draeger	Carefusion Vi-asys
Volume-targeted modes: VC (Controlled volume modes) Including decelerating flow and hybrid modes	VC PRVC SIMV (VC)+PS SIMV (PRVC)+PS Automode (VC)	A/C-VC, A/C-VC+ SIMV-VC	(S)CMV (S)CMV+ APV _{CMV} SIMV SIMV+ APV _{SIMV}	VC-CMV VC-AC IPPV SIMV SIMV/ASB	Vol A/C PRVC A/C Vol SIMV
Pressure-targeted modes PC (Controlled pressure modes)	PC SIMV (PC)+PS Automode (PC)	A/C-PC SIMV-PC	P-CMV PCV+ P-SIMV PSIMV+	PC-CMV PC-AC PC-SIMV PC-BIPAP BIPAPAssist BIPAP/ASB	Pres A/C Pres SIMV
APRV	BI-vent	Bi-Level	APRV	PC-APRV	APRV/BiPhasic
Spontaneous	PS/CPAP VS NAVA	PS SPONT VS CPAP PAV (proportional assist ventilation)	VS SPONT DuoPAP nCPAP-PS NIC NIV-ST	SPN-CPAP/PS SPN-CPAP/VS ASB SB MMV SPN-BIPAP SPN-PPS (proportional pressure support)	CPAP/PSV Vsync
Auto			ASV INTELLiVENT		

For volume-targeted modes, study personnel will record:

- Set tidal volume AND Set respiratory rate OR
- Set Minute Ventilation
- Set PEEP
- Set F_IO₂

For pressure-targeted modes, study personnel will record:

- Set pressure
- Set inspiratory time or Set I:E ratio
- Set respiratory rate
- Set PEEP
- Set F_IO₂

For APRV modes, study personnel will record:

- Set P_1 or P_{high}
- Set P_2 or P_{PEEP}
- Set T_1 or T_{high}
- Set T_2 or T_{PEEP}
- Set F_{IO_2}

For spontaneous modes, study personnel will record:

- Set pressure OR
- Set tidal volume OR
- Set minute ventilation
- Set PEEP
- Set F_{IO_2}

The following MEASURED variables will be collected for all modes:

- Tidal Volume (enter Release Volume for APRV modes)
- Respiratory rate
- Minute Ventilation
- S_pO_2
- Plateau Pressure
- Peak Inspiratory Pressure
- Mean Airway Pressure
- I:E ratio

We will use the same modified, simplified version of the ARDS Network lung protective lower tidal volume strategy as was used in the PETAL ROSE trial ⁶. This strategy, which was associated with unprecedented low mortality rates in three previous ARDS Network trials (ARMA, ALVEOLI, and FACTT), will ensure that study subjects receive the beneficial effects of lung protection as part of their participation in this trial. If not already being used, the low tidal volume ventilation protocol will be initiated within 2 hr of randomization. For those patients who remain hospitalized and on mechanical ventilation, the ventilator and weaning protocols will be implemented up to day 28 of hospitalization.

We will also use the same higher PEEP/lower F_{IO_2} strategy used in the ROSE trial ⁶ (Table 3). The use of the higher PEEP/lower F_{IO_2} protocol will be required for up to 5 days after randomization. This strategy has been repeatedly shown to improve oxygenation and to be safe.

1. Since the subjects in the TH arm will be receiving neuromuscular blockade (NMB) during cooling and rewarming, controlled modes of ventilation will be required during the ~54 hr therapeutic intervention period in both arms (except for spontaneous breathing trials in the control arm) to avoid a potentially confounding difference in ventilation strategy between arms. Following the intervention period and after NMB has ended, any mode of ventilation capable of delivering the prescribed tidal volume (V_T ; 6 ± 2 ml/kg PBW) may be used, provided the V_T target is monitored and adjusted appropriately. During APRV, tidal

volume is defined as the sum of the volume that results from the ventilator pressure-release and an estimation of the average spontaneous V_T .

2. V_T Goal: 6 ± 2 ml per kg Predicted body weight (PBW). PBW is calculated from age, gender, and height (heel to crown) according to the following equations:
 - Males: $PBW \text{ (kg)} = 50 + 2.3 [\text{height (inches)} - 60]$
 - Females: $PBW \text{ (kg)} = 45.5 + 2.3 [\text{height (inches)} - 60]$
3. Recommend measuring inspiratory plateau pressure (Pplat) according to ICU routine at least every 6 hrs and after changes in V_T and PEEP.
4. If Pplat is persistently > 30 cm H₂O, reduce V_T to 4 to 5ml/kg PBW with goal of reducing Pplat to ≤ 30 cm H₂O.
5. If $V_T < 6$ ml/kg PBW and Pplat < 25 cm H₂O, consider increasing V_T by 1 ml/kg PBW increments to a maximum of 6 ml/kg as long as Pplat < 30 cm H₂O.
6. If "severe dyspnea" (more than 3 double breaths per min or airway pressure remains at or below PEEP level during inspiration), then raise V_T to 7 to 8 ml/kg PBW as long as Pplat remains below 30 cm H₂O. If Pplat exceeds 30 cm H₂O with V_T of 7 to 8 ml/kg PBW, then revert to lower V_T and consider more sedation.
7. If pH < 7.15 , V_T may be raised and Pplat limit suspended (not required).
8. Oxygenation target: $55 \text{ mmHg} < PaO_2 < 80 \text{ mm Hg}$ or $88\% < SpO_2 < 95\%$. When both PaO_2 and SpO_2 are available simultaneously, the PaO_2 criterion will take precedence.
9. Minimum PEEP = 5 cm H₂O; lower levels allowed during weaning
10. Adjust F_{iO_2} or PEEP upward within 5 min of consistent measurements below the oxygenation target range
11. Adjust F_{iO_2} or PEEP downward within 30 min of consistent measurements above the oxygenation target range.
12. The below high PEEP strategy F_{iO_2} /PEEP table, modified from the ROSE trial ⁶, should be used in all patients with exceptions in limited situations* (Table 3).

Table 3: F_{iO_2} and PEEP guidelines

F_{iO_2}	0.30	0.40	0.50	0.60	0.70	0.80	0.90	1.0
PEEP (cm H ₂ O) ¹	5	5-16	16-20	20	20	20-22	22	22-24

¹Levels of PEEP represent levels set on the ventilator, not levels of total-PEEP, auto-PEEP, or intrinsic-PEEP)

13. No specific rules for respiratory rate, but incremental increase to maximum set rate of 35 if pH < 7.30 .
14. No specific rules about Inspiration: Expiration (I:E) ratio. Recommend I:E ≤ 1 .
15. Bicarbonate is allowed (neither encouraged nor discouraged) if pH < 7.30 .

Changes in more than one ventilator setting driven by measurements of PaO_2 , pH, and P_{plat} may be performed simultaneously, if necessary.

*We will allow deviation from the high PEEP strategy, for the following situations:

1. If there is clinical concern that the use of high PEEP may be worsening oxygenation and $F_{iO_2} \geq 0.5$ for more than 2 hrs, a trial lower PEEP may be performed.
 - If oxygenation worsens or is unchanged at the lower level of PEEP, the PEEP should be returned to the previous level.
 - If oxygenation improves, the clinicians may choose to leave the PEEP at the lower level. Subsequently the clinician should decrease the F_{iO_2} as tolerated until a listed combination on the PEEP/ F_{iO_2} chart is reached, and then continue to follow the PEEP/ F_{iO_2} protocol.
2. If hypotension, high plateau pressure (> 30 cm H₂O), and/or severe acidemia ($pH < 7.15$) are present despite further tidal volume reduction, fluid boluses, and/or respiratory rate increase, a trial of lower PEEP may be performed by reducing PEEP by 2 cm H₂O every 5-15 mins, until the physiologic parameters of concern have improved. As the patient's condition allows, a return to the study PEEP/ F_{iO_2} should be attempted through study day 5.
3. Lower PEEP may also be used if a study participant develops a pneumothorax, or is deemed at high risk for barotrauma (e.g., known multiple pulmonary cysts or bullae).

5.6 Weaning Protocol

5.6.1 Schedule for weaning assessment

Patients will be assessed at least once daily as close to 0800 as possible for the following weaning readiness criteria, but may be delayed or deferred if extenuating circumstance (e.g. off-unit procedures/surgery).

1. At least 12 hr post-randomization for the control arm and after completion of the cooling protocol and rewarming to $\geq 36^\circ\text{C}$ for the TH+NMB arm.
2. $F_{iO_2} \leq 0.40$ and $PEEP \leq 8$ cm
3. Values of both PEEP and F_{iO_2} are lower than values from previous day
4. Systolic arterial pressure ≥ 90 mm Hg without vasopressor support (≤ 5 mcg /kg/min dopamine or dobutamine will not be considered a vasopressor).

5.6.2 Spontaneous breathing trial (SBT) and ventilation liberation procedures

1. If criteria 1- 4 above are met, the NMB agent will be discontinued if it is still being infused. When the NMB has worn off and the patient is having spontaneous respirations, then initiate a trial of 30 to 120 min of spontaneous breathing with $F_{iO_2} < 0.5$ using any of the following approaches:
 - a. Pressure support ≤ 5 cm H₂O, $PEEP \leq 5$ cm H₂O
 - b. CPAP ≤ 5 cm H₂O
 - c. T-piece
 - d. Tracheostomy mask
2. tolerance will be monitored using the following:
 - a. $SpO_2 \geq 90\%$ and/or $PaO_2 \geq 60$ mmHg
 - b. Mean spontaneous tidal volume ≥ 4 ml/kg PBW (if measured)
 - c. Respiratory Rate ≤ 35 breaths/min, $pH \geq 7.30$ (if measured)

d. Absence of respiratory distress (defined as 2 or more of the following):

- i. Heart rate $\geq 120\%$ of rate prior to the SBT and lasting for >5 min
- ii. Marked use of accessory muscles
- iii Abdominal paradox
- iv. Diaphoresis
- v. Marked subjective dyspnea.

(Note: criteria ii – iv are often described as “respiratory distress” or “increased work of breathing” in the EMR.)

- 3. If all 4 measures of tolerance are not met, revert to previous ventilator settings or to PS +10 cm H₂O with Positive End-expiratory Pressure and F_IO₂ = previous settings and reassess for weaning the next morning.
- 4. The clinical team may decide to change mode of support during spontaneous breathing (PS = 5, CPAP, tracheostomy mask, or T-piece) at any time.

5.6.3 Decision to remove ventilatory support

- 1. For intubated patients, if the four tolerance criteria for SBT are met for at least 30 min, the clinical team may decide to extubate. However, the spontaneous breathing trial can continue for up to 120 min. if tolerance remains in question. If all 5 tolerance criteria are not met during unassisted breathing (or 120 min has passed without clear tolerance), then the ventilator settings will be reset to the settings used just prior to the weaning and the patient will be reassessed for weaning (see section 5.6.1) the following day.
- 2. Unassisted breathing is defined as any of the following:
 - a) Extubated with face mask, nasal prong oxygen, or room air
 - b) T-tube breathing
 - c) Tracheostomy mask breathing
 - d) CPAP ≤ 5 cm H₂O without PS or IMV assistance
 - e) Use of CPAP or BIPAP solely for sleep apnea management
 - f) Use of a high flow nasal cannula oxygen system
- 3. Patients will be considered to have completed the study ventilator procedures if any of the following conditions occur:
 - a. Death
 - b. Hospital discharge
 - c. Alive 28 days after randomization

4. If a patient requires positive pressure ventilation after a period of unassisted breathing, the study ventilator procedures will resume unless the patient is discharged from the hospital or >28 days elapsed since randomization.

5.7 Decision to transition to ECMO

1. Decision to transition to ECMO will be made based on the clinical judgement of the primary intensivist.
2. The start and stop dates for ECMO will be recorded. ECMO status will not affect any CHILL protocols or CHILL data collection, including unassisted breathing and ICU discharge data or calculation of 28-day Ventilator-free days and 28-day ICU-free days.

5.8 Lung Transplantation

1. Lung transplantation prior to study day 90 will be considered equivalent to death for statistical analysis.
2. If patients undergo lung transplantation within the first 28 days of the trial, the "Lung Transplant box on form F99 (Patient Status) will be checked form F91 (Lung Transplant) will be completed. The day 28 form will be completed indicating 0 for Ventilator-free days and for 28-day ICU-free days. No additional data will be collected.
3. If patients undergo lung transplantation after day 28, form F91 will be completed. No additional data will be collected.

6.0 Study Interventions

6.1 Therapeutic Hypothermia Arm:

- Adjust sedation to Richmond Agitation-Sedation Scale (RASS) -4 or -5, Ramsay score 5 or 6, or Riker 1 or 2, then start continuous NMB with continuous infusion of vecuronium, cisatracurium, atracurium, or other NMB agent based on institutional and investigator preference. Intermittent dosing will be allowed as long as continuous NMB effect is maintained.
- If adjusting the NMB dose based on neurostimulatory monitoring, the NMB infusion rate will be adjusted to achieve two twitches on train-of-four testing and further adjusted to eliminate detectable shivering.
- If a fixed dose is used without neurostimulatory monitoring, the NMB infusion rate will be adjusted to eliminate detectable shivering.
- Once sedation and NMB are confirmed, hypothermia to 34°-35°C will be achieved as quickly as possible, preferably within 6 hrs of randomization, using one of several available FDA-approved surface cooling devices.
- Temperature will be measured continuously from a central probe (esophageal, urinary, or intravascular).

- Once the target temperature is reached, it will be maintained as close as possible to 34-35°C for 48 hrs. If the patients fail to reach target temperature by 54 hr after randomization, cooling will be halted and, if core temperature <36°C, rewarming initiated as described below.
- Subjects will then be rewarmed to 36°C by 0.3±0.2°C per hr and the cooling devices will then be removed.
- NMB will then be discontinued unless the ICU team feels there is clinical indication for continued NMB (e.g. ventilator desynchrony).
- Following the 54 hr treatment period (including cooling and rewarming time), temperature management in both arms will be directed by the ICU team.

6.2- Usual Temperature Management Arm:

- Based on the control group protocol in the ROSE trial, the subjects in the Usual Temperature will receive light sedation with RASS -1 or 0, Ramsay score 2 or 3, or Riker 3 or 4 and no NMB but additional sedation and NMB are allowed if clinically indicated.
- During the 54 hr post-randomization period (corresponding with cooling period TH arm (6 hrs to achieve cooling + 48 hrs at the target temperature), acetaminophen and/or surface cooling may be used to treat fever >38.5°C with goal of maintaining core temperature ≤38.5°C; administration of anti-shivering therapy will be per standard of care at the discretion of the ICU providers.
- If subjects are hypothermic (core temperature ≤36°C) during CRRT, surface warming will be used to restore core temperature to approximately 37°C.
- Following the 54 hr treatment period (including cooling and rewarming time), temperature management in both arms will be directed by the ICU team.

6.3 Research Blood Collection

Two EDTA 6ml purple (or pink) top tubes (total 12 ml blood) will be collected at the following times;

Baseline: Collect immediately prior to randomization,

Study Day 1: Collect as close to 0800 as possible

Study Day 2: Collect as close to 0800 as possible

Study Day 3: Collect as close to 0800 as possible

Study Day 4: Collect as close to 0800 as possible

Study Day 7: Collect as close to 0800 as possible

See Secondary Endpoints (Section 7.2) for description of planned biomarker analysis. Unused samples will be stored for at least 6 yrs after study completion for additional analyses by CHILL investigators and other qualified investigators. The samples will not be subjected to nucleic acid sequencing.

6.4 Assessment of Vital and Functional Status

Data on vital and functional status will be collected at ICU discharge, study day 28, hospital discharge, study day 60 and 90. If patient is discharged, a phone call will be placed to obtain vital and functional status after patient hospital discharge. If patient is alive but unable to provide information, a caregiver can provide needed information.

7.0 Study Endpoints:

7.1 Primary Endpoint:

The primary endpoint for CHILL is a composite of rank-transformed 28-day VFDs for those who survive to day 28 and worst ranks assigned to those who die by day 28 according to day-time of death (hereafter, 'worst-rank scores'). Twenty-eight-day VFDs was chosen because: (1) it has been used as a secondary outcome in most Phase III ARDS trials, including ARMA, ACURASYS, and PROSEVA; (2) it is a predictor of both survival and lung function; (3) we found a significant effect size of TH on 28-day VFD compared with historical controls in our CHILL-pilot study, and (4) it is relevant to clinical practice guidelines for the immediate care and transport of critically ill or injured military. We realize that VFDs can be biased by physician decision-making about transitioning to unassisted breathing and by confounding factors that prolong respiratory failure. We have addressed these potential pitfalls by protocolizing and monitoring decision-making regarding liberation from mechanical ventilation and by excluding conditions that may independently reduce VFDs (e.g. active hematologic malignancy, severe underlying lung disease, cardiomyopathy). Details will be documented in the Transition to Unassisted Breathing form (F31). The 28-day VFDs will be calculated at day 28 and recorded on the day 28 CRF. For subjects still alive after 28 days, the 28-day VFD is calculated by adding the number of Unassisted Breathing days in the 28 days post-enrollment period. Transient Unassisted Breathing time will be included as long as the subject was continuously breathing without assistance for ≥ 48 hrs. VFDs for subjects who die by day 28 will be recorded as missing and date-time of death will be recorded in order to construct the worst rank score composite outcome. Lung transplants will be treated as deaths in all analyses.

7.2 Secondary Endpoints:

Clinical: (a) 28-day ICU-FDs; (b) SOFA scores at baseline and study days 1-4 and 7; (c) 60- and 90-day functional and vital status; (d) 90-day functional status; and (e) hospital, 60-day, and 90-day mortality. SOFA scores for days 1-3 will exclude the neurologic component when subjects in the TH arm will be receiving NMB. Decisions about transfer out of the ICU will be protocolized.

Physiologic: (a) changes in driving pressure ($P_{\text{plat}} - \text{PEEP}$ during non-patient-initiated breath) between baseline and study days 3 and 7; (b) changes in oxygen saturation index (OSI; $\text{Mean airway pressure} \times 100 \times F_{\text{I}}\text{O}_2/\text{SpO}_2$) between baseline and study days 3 and 7.

Biomarker: The plasma biomarkers measured on study days 0, 1, 2, 3, 4, and 7 were selected to provide insight into mechanism of TH effect on ARDS pathogenesis and includes: IL-6 and 8 (marker of inflammation; predictive of survival in reanalysis of ARMA and ALVEOLI data), IL-1 β

and 18 (products of inflammasome activation, an indicator of p38 activation), soluble-RAGE and surfactant protein (SP)-D (indicator of Type I and II alveolar epithelial injury), soluble ICAM-1 (indicator of endothelial activation/injury), MMP8 (marker of neutrophil activation; elevated in ARDS), and sTNFRI. Unused samples will be stored for at least 6 yrs after study completion for additional analyses by CHILL investigators and other qualified investigators. We will also measure Protein C at baseline to support subgroup analysis based on ARDS subtype (defined by levels of IL-8, bicarbonate, and protein C).

Safety: Safety measures to be monitored for the first 54 hrs (during cooling and rewarming), based on the post-cardiac arrest experience, include: (a) continuous cardiac monitoring for bradycardia and arrhythmias; (b) every 6 hr point of care (POC) blood glucose monitoring; (c) every 12 hr serum potassium, magnesium and phosphate measurement and (d) monitoring for significant bleeding event (requiring ≥ 3 u packed red blood cells or surgical/interventional radiologic intervention). Based on the theoretical concern for immunosuppression, we will monitor for VAP and other secondary infections during the first study week.

8.0 Guidelines for Developing Order Sets

Please develop order sets tailored to your institutional policies, equipment, and formulary using the following guidelines:

Monitoring (both groups):

For first 96 hours:

Record core temperature at least every 2 hours

Record SpO₂ and associated FiO₂ and mean airway pressure at least every 2 hours

Record POC glucose at least every 6 hours

Obtain 6 ml two purple/pink top research blood samples at ~0800 and place on ice.

Send comprehensive metabolic panel each morning, CBC each morning and evening, and basic metabolic panel each evening

Record Glasgow coma score daily

For study days 5 – 7:

Record SpO₂ and associated FiO₂ and mean airway pressure at least every 6 hours

Send daily CBC and comprehensive metabolic panel

For study day 7:

Record Glasgow coma score

Obtain 6 ml two purple/pink top research blood samples at ~0800 and place on ice.

For Control Arm:

For first 54 hours

Maintain sedation with RASS goal -1

Warming blanket set to 37°C for core temperature <36°C

Acetaminophen for core temperature >38.5°C

(clinical discretion for adding cooling devices and treating shivering)

Start daily screening for Spontaneous Breathing Trials beginning 12h post-randomization

For Hypothermia Arm:

Adjust sedation to achieve RASS -5

Start neuromuscular blocking agent to achieve 2 twitches on train-of-four testing (if using) and adjust to eliminate obvious shivering.

Once neuromuscular blockade is achieved, start cooling to target core temperature 34° - 35°C and maintain for 48 hours.

48h hours after initially reaching the target temperature, rewarm at 0.1 to 0.5°C per hour until reaching 36°C, then remove cooling device.

Once core temperature reaches 36°C, discontinue neuromuscular blocking agent and note time required for neuromuscular recovery

Reduce sedation to clinically indicated level

Once patient has rewarmed and recovered neuromuscular function, start daily screening for spontaneous breathing trials.

9.0 Schedule of Events

Study Day	Screening/ Enrollment	Randomiza- tion	Day 1	Day 2	Day 3	Day 4	Day 7	Days 8-27	Day 28	ICU DC	Hospital DC	Day 60	Day 90
Procedures time window	up to 7 days		8-32 hrs post randomiza- tion to 0800	24 hrs To 0800	24 hrs To 0800	24 hrs To 0800	24 hrs To 0800						
Screening, consent, enrollment, monitor for randomization	X												
Pregnancy (F)	F												
Randomization, Base-line data, start as- signed temperature management		X*											
Q2hr vital signs (e.g. SpO2, mean airway pressure, core temperature)		X	X	X	X	X							
Temperature man- agement Protocol		X	X	X	X**								
ABGS		A	A	A	A	A	A						
AM CMP and CBC		X	X	X	X	X	X						
PM BMP, phos, Mg			X	X	X								
Blood Sugar (times per day)		1	4	4	4	A	A						
Research Blood Col- lection		X***	X	X	X	X	X						
Ventilator and respir- atory parameters	X	X	R	R	R	R	R						
Fluid management			X	X	X	X	X						
NMB Status	X	X	X	X	X	X	X						
Medication review (steroids, inhaled vasodilators)		X	X	X	X	X	X						
Monitor AEs			X	X	X	X	X	X	X	X	X	X	X
Calculation 28-day VFDs, ICU-FDs									X				
Assess Vital and Functional Status			X	X	X	X	X	X	X	X	X	X	X

*= Baseline data collection from 24 hrs prior to randomization.

** The number of hrs in day 1 (8-32) depends on Randomization time. All other days are 24 hrs.

*** immediately prior to randomization, only collect when randomization is imminent.

A= When available

X = Required (time not specified)

R= Measure during daily reference measurements (0600-1000). When more than one value is available, the value obtained closest to 0800 will be recorded.

F = Required on females with reproductive potential.

10.0 Study Associated Risks and Risk Mitigation

Although not expected to occur with modest TH to 34°-35°C, patients can develop:

(1) persistent severe bradycardia (heart rate <30 associated with mean arterial pressure <65 mm Hg without vasopressors); (2) uncontrolled bleeding and (3) intractable ventricular arrhythmias. In the event any of these conditions happens, TH protocol will be terminated early following clinical guidelines. (4) There is a slightly increased risk of infection, study subjects are closely monitored for infection and the appropriate use of antibiotics should be initiated as standard of

care. (5) There is a mild risk of changes in fluid and electrolyte balance, but this patient population is closely monitored and correction will be implemented as standard of care. (6) There is a mild to moderate risk of hyperglycemia occur, but this patient population is closely monitored and correction will be implemented as standard of care. (7) There is a slight reduction in the ability of blood clotting mechanism, but this patient population is closely monitored and corrections will be implemented as standard of care.

10.1 Guidelines: Managing Bradycardia during Therapeutic Hypothermia:

Prevention:

1. Avoid dexmedetomidine (see Tobias; J. Intensive Care Medicine 2008; 23:403-408 for example of 2 case reports).
2. Hold other meds that reduce heart rate if possible (e.g. beta blockers; calcium channel blockers).

Treatment:

1. Bradycardia is a predictable response to hypothermia due to temperature-dependence of diastolic repolarization in the cells of the sinus node. A heart rate of 40 is normal at 32°C in otherwise healthy adults. The risk of clinically significant arrhythmias is very low with core temperature >30°C.
2. The AHA recommends no treatment for the bradycardia if the patient remains normotensive (or there is not an increase in pressor requirement).
 - a. Check 12-lead EKG to assess rhythm.
 - b. Check electrolytes
 - c. Check meds for possible interactions or additive effects
 - d. Slowly adjust core temperature closer to 35°C
3. If bradycardia is accompanied by hypotension or increase in pressor requirement.
 - a. Check 12-lead EKG to assess rhythm.
 - b. If unsure of rhythm, consult with Cardiology
 - c. Check electrolytes
 - d. Check meds for possible interactions or additive effects
 - e. Treat with pressor that has inotropic and chronotropic effects (e.g. norepinephrine or epinephrine).
 - f. Check volume status (POCUS).
 - g. Slowly rewarm toward 35°C.
 - h. If still bradycardic and hypotensive persist slowly rewarm until hypotension resolves.
 - i. Consider rechallenging once patient stabilizes and volume and electrolytes are optimized.

11.0 Adverse Event Reporting

Adverse events will be classified according to the following definitions (21 CFR 312.32):

11.1 What is not an Adverse Event

Organ failures or death related to ARDS or the patient's underlying condition that are systematically captured by the protocol (primary or secondary outcomes) should not be reported as AEs unless they are considered study-related.

11.2 Severity

This is graded as Grade 1-5:

- Grade 1: Mild; asymptomatic or mild symptoms without need for intervention
- Grade 2: Moderate; symptomatic; minimal, local or noninvasive intervention indicated
- Grade 3: Severe; medically significant but not immediately life-threatening; prolongation of critical illness; disabling
- Grade 4: Life-threatening; urgent intervention indicated.
- Grade 5: Death related to AE

11.2.1 Table 4. Grading of possible intervention-associated metabolic abnormalities:

Adverse event	Grade (LLN = lower limit of normal) ¹				
	1	2	3	4	5
Hypokalemia	3.0 mmol/L-<LLN asymptomatic	3.0-LLN mmol/L symptomatic	2.5-2.9 mmol/L	<2.5 mmol/L	Death
Hypomagnesemia	1.2 mg/dL-<LLN	0.9-<1.2 mg/dL	0.7-<0.9 mg/dL	<0.7 mg/dL	Death
Hypophosphatemia	2.5 mg/dL-<LLN	2-<2.5 mg/dL	1.0-<2.0 mg/dL	<1.0 mg/dL	Death
Hyperglycemia	160 mg/dL->ULN	>160-250 mg/dL	>250-500 mg/dL	>500 mg/dL	Death

¹ Columns 1-3 (Grade 1-3) of tables will be tabulated as data but not AEs (can add to DSMB report). Column 4 for all four are AE's. For K and Mg, column 4 and life-threatening arrhythmia or glucose and DKA (clinical judgement in chart), phosphate (unexplained coma, weakness, rhabdomyolysis, seizures) are SAEs. Maybe better to omit the slide.

11.3 Serious

This will be reported as "Yes" or "No." An AE will be classified as serious if it is fatal or immediately life-threatening (as the reaction occurred, not if it had occurred in a more serious form), permanently disabling, severely incapacitating, or requires or prolongs inpatient hospitalization. Events that may jeopardize the patient and require medical or surgical intervention to prevent one of the previously listed outcomes may also be classified as serious.

11.4 Unexpected

AEs will be classified as either expected or unexpected. An AE will be considered unexpected if it is not listed in the protocol or not listed at the specificity or severity observed, or not consistent with the risk information described in the general investigational plan, or that in unexpected in the course of treatment for ARDS.

Expected disease-related complications (not reported as SAEs):

Neuro: Delirium

CV: Circulatory shock, distributive or cardiogenic (unless investigator feels is related to cooling)
Cardiac arrest, PEA (unless related to hypokalemia during cooling)

Pulmonary: Progressive respiratory failure; Fibrosis; Barotrauma (pneumothorax, pneumomediastinum); Ventilator-associated pneumonia; Failure to wean from ventilator

Renal: AKI; Metabolic acidosis or alkalosis; Asymptomatic electrolyte disorders

GI: GI bleeding (exception under heme); Ileus; Diarrhea; Malnutrition

Endocrine: Hyperglycemia (except for exclusion noted in Table 5); Hypoglycemia

Heme: Anemia; Leukocytosis; Thrombocytopenia; Coagulopathy (unless coagulopathic severe bleeding during cooling)

ID: Most infections

Expected Complications that should be reported as SAE:

CV: V-fib or V-tach cardiac arrest during cooling, especially if associated with hypokalemia; Symptomatic bradycardia; limb ischemia that started during cooling

Renal: Severe symptomatic electrolyte disorders during cooling resulting in life threatening arrhythmia

Heme: Coagulopathic life-threatening hemorrhage during cooling

Neuro: CNS hemorrhage first noted during cooling or in subsequent 36 hrs.

11.5 Study-related

AEs will be considered to be study-related if the event follows a temporal sequence from a study procedure and could have been produced by the study procedure. Study relatedness will be classified as follows:

1. Not related: not associated with the investigational procedure
2. Unlikely: unlikely to be associated with the investigational procedure
3. Possible: possibly associated with the investigational procedure
4. Probable: probably (>50% likelihood) associated with the investigational procedure
5. Definite: definitely associated with the investigational procedure

11.6 Reporting requirements

The following will be reported to the DSMB within 5 business days of the investigator becoming aware of the information:

1. Information that indicates a new or increased risk.
2. Any harm experienced by a subject or other individual which in the opinion of the investigator is **unexpected** and at least **probably related** to the investigation and places subjects or others at a greater risk of harm than was previously known or recognized.
3. Non-compliance with federal regulations governing human research, or with the requirements or determinations of the IRB, or allegations thereof.
4. Failure to follow the protocol due the action or inaction of the investigator or research staff
5. Breach of confidentiality
6. Change to the protocol with prior notification of the IRB to avoid an immediate hazard to a research subject
7. Incarceration of a subject
8. Complaint of a subject or authorized representative that cannot be resolved by the research team.
9. Suspension or termination of the research by the sponsor or the investigator.

10. Unanticipated adverse device effect

Any deaths or life-threatening or hospital-course-prolonging events that are unexpected or temporally related with study procedures, including cooling and rewarming, will be reported within 24 hrs to MVS. Site personnel will fill out the paper SAE reporting form (F30) and send a pdf of the form without direct patient identifiers (the CHILL ID number is required) to MVS as an email attachment to pv@cchmc.org. MVS will contact the site and assure that all patient data required for analysis of the SAE, including the site PI's assessment of severity and study-relatedness, are submitted. If the AE is severe and related to the study, MVS will notify the CHILL Independent Research Monitor, Dr. Michael Mazzeffi. If the event is assessed to be unrelated, the event will be added to the monthly report prepared for Dr. Mazzeffi. If Dr. Mazzeffi requires additional information related to the SAE, he will send a request to MVS rather than contact the site directly. The information regarding the event will be entered into the eDC and signed off electronically by the site PI or a designated alternate investigator. Dr. Mazzeffi will monitor the monthly reports and individual SAEs for patterns of SAEs that suggest potential problems with subject safety. He will report these to the DSMB Chairman, Dr. Shelhamer with Dr. Terrin copied on the communication. Otherwise, the monthly tabular report will be sent to Dr. Terrin with Dr. Mazzeffi's statement that he has no concerns. Dr. Terrin will send a copy of the tabular report to Dr. Shelhamer for the record. The DSMB will evaluate reports received from the independent research monitor suggesting potential problems with subject safety. If the DSMB members agree concur that the pattern is problematic to the point of being actionable, the DSMB members will specify the action they favor (e.g. discuss with CEC; put the clinical trial on a pause and to review all recorded events immediately; stop the clinical trial immediately) and notify the CEC, the central IRB, and DoD HRPO. The CHILL leadership will act promptly on any safety concerns. If difference(s) between treatment groups in the lesser AEs are a concern, Dr. Mazzeffi may recommend individual review of a group of AE cases. Dr. Terrin will submit tabular summaries of all AEs to the DSMB with DSMB reports approximately every 6 months for review and discussion at their biannual meetings.

12 Statistical Design and Power

12.1 Sample Size and Stratification Plan

Using PASS v. 11 sample size software, we estimated the needed sample size by simulating our composite endpoint and using the Wilcoxon-Mann-Whitney (WMW) test of treatment arm difference. We seek to have power to detect a 4-day reduction in 28-day VFDs as defined and detected in the PROSEVA trial. To simulate the worst-rank score distribution in the control arm (and CHILL arm under the null hypothesis) we assumed a 28-day mortality rate of 32%, approximately equal to the rate in the control group of the PROSEVA trial and in the historical control group in our prior pilot study (n=58). We estimated another 32% of the control arm would survive to day 28 but have zero 28-Day VFDs (consistent with our pilot data) and that the distribution of 28-Day VFDs in the remaining 36% of the control arm would be uniform with mean 28-Day VFDs equal to 15 (as in our pilot study control group). For the CHILL arm we reduced the

mortality rate and number with 28-Day VFDs = 0 by nine percentage points, and increased the number of 28-Day VFDs among the remainder in order to simulate an overall 4-day increase in 28-day VFDs as defined and achieved in the PROSEVA trial. With the above parameter settings, power set to 90% and alpha-level set to 0.05, the initial sample-size estimate for the WMW test applied to worst rank scores equaled 258 (129 per group). The sample size was then corrected to allow 10% one-way crossover assuming that subjects randomized to hypothermia may not receive study treatment because of technical issues but that subjects randomized to standard treatment would not likely receive hypothermia treatment. The 10% is conservative (resulting in a larger total N) as the cross-over is typically ~3-4% in similar trials. This adjustment resulted in a sample size equal to $129/(1-.10)^2 = 162.0$ per group. Hence, the final total N = 320. Because this estimate is very close to a prior estimated sample size of 324 used in planning the study, we are retaining the final total N = 324.

12.2 Data Analysis Plan

12.2.1 General Considerations:

12.2.1.1 *Intention to Treat*

Primary and secondary analyses will be performed according to the principle of intention-to-treat, including all randomized patients, analyzed by treatment assigned at randomization.

12.2.1.2 *Per-Protocol Population*

As part of assessing the feasibility of a Phase III clinical trial, additional per protocol analyses according to the treatment received by the patients will also be performed. The per-protocol population will include only randomized patients who: (1) are alive 54h after randomization; (2) either complete 28 days of follow-up with assessed 28-Day VFDs or who die within 28 days of randomization; and (3) for patients in the TH+NMB arm, that core temperature not exceed 35°C for at least 20 of 24 contiguous 2-hour blocks during the 48h TH treatment period.

12.2.1.3 *Strata and Covariates*

The randomization is stratified only by site, which will be accounted for in the primary efficacy analysis.

12.2.1.4 *Multiple Comparison*

For the primary analysis, we consider a two-sided p-value of 0.044 to be significant. It is less than 0.05 to account for the interim analyses. To account for the multiplicity of hypotheses being tested in secondary and exploratory analyses, a p-value < 0.01 will be required to consider there to be evidence of differences present, i.e., to reject the null hypothesis. We consider $p < 0.001$ as strong evidence.

12.2.2 Interim Analyses:

Three interim analyses will be performed after ~25% (n=81), ~50% (n=162), and ~75% (n=243), of planned enrollment has either been followed-up for 28 days or have died prior to the 28th day. The primary statistical analysis method (stratified Wilcoxon-Mann-Whitney test comparing worst ranks scores), including how rank scores will be assigned for cases of lost to follow-up or withdrawal will be performed in the same way as for the final primary analysis. As the primary

statistical analysis method requires each site to have randomized at least three patients and at least one to each treatment group, all sites that haven't met this requirement will be combined into a single conglomerate site for analysis purposes. To inform the decision whether to stop the trial early due to superiority of the TH treatment arm (greater 28-Day VFD's), we will use the Lan-DeMets⁹ alpha spending function with O'Brien-Fleming-like¹⁰ upper boundary. The spending function is:

$$\alpha(t^*) = 2 - 2\Phi(Z_{\alpha/2}/t^*)$$

where $t^* = n[n_{CH}^{-1} + n_{UTM}^{-1}]^{-1}/[N_{CH}^{-1} + N_{UTM}^{-1}]^{-1} = [n_{CH}^{-1} + n_{UTM}^{-1}]^{-1}/81$ and n_{CH} and n_{UTM} equal to the interim sample sizes of the two arms and total $N = N_{CH} + N_{UTM} = 162 + 162 = 324$ ^{11,12}. As calculated using PASS v.11, the z critical values (cv's) that much be equaled or surpassed by the stratified WMW z test statistic are provided in the table below under Upper Boundary for $t^* = .25, .50$, and $.75$. To account for sequential testing, rejecting the null hypothesis favoring TH after completion of the study requires the Z test statistic to surpass 2.01406 in the primary efficacy analysis. To inform the decision to stop the trial early due to harm, we propose to use the approximate O'Brien-Fleming-like lower boundary as provided in the table below. Final boundaries will be adjusted as necessary if the interim analyses are not conducted at exactly 81, 162, and 243 cases, and/or if the final analysis is not at exactly 324 cases.

Table. Approximate Upper and Lower O'Brien-Fleming-Like Boundaries (PASS v. 11¹⁰)

Look	t*	Lower Bound-ary	Upper Bound-ary	Nominal Alpha	Alpha In-crement	Total Alpha
1	0.25	-4.33263	4.33263	0.000015	0.000015	0.000015
2	0.50	-2.96311	2.96311	0.003045	0.003036	0.003051
3	0.75	-2.35902	2.35902	0.018323	0.016248	0.019299
4	1.00	-2.01406	2.01406	0.044003	0.030701	0.050000

The trial may also be stopped early if there is evidence of futility based on the conditional probability of rejecting the null hypothesis given the “current trend” is less than 20% at the 2nd interim analysis or 3rd interim analysis. Conditional power will be calculated by normal approximation as suggested by Lan and Wittes ¹² using the formula provided on page 1026 of Chen, DeMets, & Lan (2004) ¹³. Before making a recommendation to terminate the trial, either for a beneficial effect, harm, or futility, the DSMB will consider the interim analysis results along with other relevant factors. These factors will include enrollment and study conduct, the numbers and distributions of deaths, the frequencies and distributions of other secondary outcomes, and findings from other relevant studies.

12.2.3 Demographics and Baseline Characteristics

Baseline characteristics (pre-neuromuscular blockade) by treatment group for the intention-to-treat population will be compared using counts and percentages for categorical variables. Either the mean and standard deviation or median and interquartile range (25th/75th percentiles) will be reported for continuous variables. The following baseline characteristics will be reported: Age, gender, race, ethnicity, APACHE II, P/F ratio, proning status (at baseline), steroids, shock, SOFA, PEEP (cm H₂O), renal replacement therapy, COVID, and IL-6, bicarb, and protein C biomarkers.

12.2.4 Efficacy Analyses:

12.2.4.1 Primary Efficacy Analysis

Primary and secondary analyses will be performed on the intention-to-treat (ITT) population. Per protocol analyses will also be performed as part of assessing the feasibility of a Phase III clinical trial with a longer-term mortality outcome. The primary analysis will be to test the treatment group difference on the primary endpoint, worst ranks, while accounting for site in the analysis. This will be accomplished using Wilcoxon-Mann-Whitney rank sum test extended to account for stratification by site (known as the van Elteren test¹⁴). Worst ranks for participants who are withdrawn from the study or lost to follow-up will be assigned as described in section

7.1 (Primary Endpoint). As for the interim analyses, any sites that haven't met the minimum sample size requirement (three randomizations, at least one to each treatment group) will be combined together into a single conglomerate site for analysis purposes. The alpha level of the test will be 0.05 (two-sided).

12.2.4.2 Per-Protocol Analysis

As a secondary analysis, the same analysis as performed in the primary efficacy analysis will be performed on the per protocol population. In addition, we will compare treatment groups on the primary endpoint in the per protocol population with a regression model with worst ranks as the dependent variable and treatment group and treatment center and several prognostic covariates as independent variables. Treatment center (14 sites) will be specified as a random effect. The prognostic covariates will include proning status, age, race, gender, and steroid use. However, before fitting the above model we will first examine subgroup differences by adding interaction terms between treatment group and the other independent variables. First, we will include an interaction term between treatment group and center to test whether there is significant variance in treatment effect among centers. This interaction will be random since center is random and so the global likelihood ratio test statistic for testing the interaction would be compared to a weighted mixture of two chi-square distributions¹⁵. If significant ($p \leq 0.05$), we will retain this interaction term in the above regression model and estimate and report treatment effects by center (coded). Second, we will add the interaction term between treatment group and each of the above baseline prognostic variables and if any are significant, we will estimate and report treatment effects by identified subgroups.

12.2.4.3 Subgroup Analyses

As a secondary analysis of the intent-to-treat analysis population, heterogeneity of treatment effect on the primary endpoint across levels of baseline patient characteristics will be assessed with a global test of interaction using a linear regression model. Independent terms in this model will include treatment group, baseline characteristic variable, and the interaction between treatment group and baseline characteristic variable. Baseline characteristic can be either categorical or continuous. A significant interaction (two-sided $p \leq 0.05$) will be followed by an estimate of treatment effect and 95% confidence interval for each level of categorical subgroups. *A priori* baseline characteristics to be tested include: proning status, shock, COVID, P/F ratio, age, time between initially meeting moderate to severe ARDS criteria and randomization, and baseline biomarkers (IL-6, bicarb, and protein C).

12.2.5 Interpreting Analysis Results

Interpretation of the primary outcome analysis must be cognizant of CHILL as a Phase IIb clinical trial. The primary outcome is intermediary to the ultimate outcome of longer-term mortality. Effects on longer term mortality could be observed fortuitously and will be interpreted as a secondary outcome.

If the null hypothesis is rejected, the investigators have the responsibility to assure and explain to the medical community that bias is not the reason for rejecting the null hypothesis. If the investigators fail to reject the null hypothesis, they have the responsibility to assure that they

have performed a sensitive test and explain to the medical community their basis for believing that bias is not the reason for failing to reject the null hypothesis.

Interaction with clinical site. Influence of clinical site on treatment effects will be inspected. If there are outlier clinical sites, explanations for the inhomogeneity will be sought (e.g., differences in fidelity to the treatment protocol) and any differences or inhomogeneities found will be presented with the primary analysis.

Effect size. A recommended effect size measure after performing a Wilcoxon-Mann-Whitney test statistics is known as the “probabilistic index” (q) and is defined as the estimated probability that an individual randomly selected from the study population will have a superior outcome if assigned to the experimental treatment, in our case therapeutic hypothermia. An advantage of this measure is it is mathematically linked with the WMW test statistic. A disadvantage of this effect size measure is that it is not on a commonly used measurement scale familiar to clinicians. When the outcome is on a simple quantitative scale, group medians are commonly reported after a WMW test and are more easily interpreted. However, this may not be sufficient for composite outcomes that combines mortality with a continuous outcome measure such as worst ranks. We will, therefore, report q as an overall effect size with a 95% confidence interval, and supplement it with more clinically interpretable summary statistics of the two constituent components underlying our worst ranks primary endpoint: (1) the 28-day mortality rate in each group and (2) median 28-day VFDs among the 28-day survivors in each group. Reporting q with a 95% confidence interval after performing the equivalent of a WMW test of worst ranks and the above two summary statistics of the constituent components was the recommendation for ARDS trials in a recent article in *Critical Care Medicine*¹⁶.

In addition, we will calculate the median worst rank (including worst ranks assigned to those who died before day 28) for each group and reverse transform these values to 28-Day VFDs according to the mapping of 28-Day VFDs to worst ranks. We refer to these as “median 28-Day VFDs based on worst ranks”. Interquartile ranges will also be calculated in this way with the possible modification that the 25th percentile may correspond to death before day 28.

We will report the above effect-size measure and summary statistics in both the ITT and Per-Protocol populations. We will compare the WMW test result (p -value), effect size q , and constituent summary statistics between the two populations to further aid interpretation of the results.

13.0 Data Management Plan

Data management will be performed according to standard operating procedures promulgated by the DCC in consultation with the Clinical Coordinating Center (CCC). The data management plan developed for the CHILL trial is based on simultaneous necessity of data integrity/rigor and protection of patient confidentiality.

Data management for CHILL will be coordinated through the Department of Veterans Affairs CSPCC at Perry Point, MD under the supervision of Dr. Michael Terrin (DCC). A CHILL team

email address (CHILLdata@va.gov) has been created for correspondence with the CSPCC CHILL team to ensure correspondence is promptly reviewed.

Direct identifiers will never leave the clinical site. Screening logs, medical records and other notes containing direct identifiers are stored securely at the clinical sites. Each screened patient will be assigned unique 8-9 character alphanumeric study ID (SID) number in which the first 1-2 characters represent the site ID number followed by a unique 3-letter identifier (unrelated to initials or any other personally identifying information) and a 4-digit subject number assigned in ascending order beginning with 1001 for each site. We will document that clinical site staff who handle study data are all trained in human subjects, good clinical practice (GCP) and CHILL-specific data and specimen collection using the RAVE eDC (Medidata, Inc). During the recruitment, treatment, and follow-up phase of the CHILL trial, the clinical site staff will assemble source documents and complete hard copy forms to be kept in securely stored binders on site. They will be granted individual permissions, based on their roles within the study, to log onto the web-based CHILL electronic data capture (eDC) system to enter data from study forms. The eDC will time stamp and identify the individual entering data for all transactions on the eDC and maintain an audit trail for every data item. Select individuals with authorization to enter data will be authorized also to randomize screened patients whose baseline data are complete and who are eligible for CHILL on the web-based randomization module accessed through the CHILL eDC system.

Each data item entered on the eDC will be edited for proper character type (e.g. numeric versus alphabetic) and range at the time of entry with immediate edit messaging for those items that fail those edits. At the time of submission, forms will be edited for completeness and consistency with immediate edit messaging for those items that are incomplete or inconsistent with other data items. As much as possible, data items will be entered from drop down menus which prevent character and range errors. At regular intervals, e.g. every two weeks, the database will be edited for cross form and longitudinal consistency and receipt of expected forms with reports for the study leadership monitoring study progress as well as the clinical sites as reminders to attend to data quality concerns. Independent clinical monitors (provided by subcontractor, KAI) will visit each clinical site twice a year to verify consent form completion and eDC data against form data and source documents. At six-month intervals a data analysis file will be extracted from the database, copies of the data analysis file and frozen, database archived, and the data analysis file utilized for a DSMB report.

At the end of the study and final database cleaning, the database will be locked, and a final de-identified data analysis file will be prepared for delivery to the Department of Defense. Source documents, forms and database will be retained for seven years after database lock.

14.0 Clinical Monitoring Plan

Independent clinical monitoring will be provided by Navitas Clinical Research (NCR). NCR will conduct visits to each site every 6 month to (1) assure the rights and safety of participants; (2)

confirm study conduct follows the guidelines of E6 Good Clinical Practice: The International Conference on Harmonisation; (3) verify adherence to protocol; (4) assess recruitment efforts; (5) monitor the quality of data collected; (6) assure accurate reporting and documentation of all adverse events; (7) assess security of confidential records; and (8) address and resolve issues related to the conduct. At each visit, the clinical research associate will review the informed consent forms and baseline/eligibility forms for 100% of enrolled/randomized participants and the temperature data for study days 1 – 3, the unassisted breathing forms, data on spontaneous breathing trials and weaning, and the study day 28 form for at least 75% of enrolled/randomized participants, monitor all serious adverse event forms utilizing the discharge forms for all enrolled/randomized participants, and at the conclusion of each visit, conduct an exit interview with the site Principal Investigator that includes any problems or issues discovered and proposed approaches to resolving any outstanding issues. Should travel restrictions due to the COVID-19 pandemic preclude in-person visits, we will arrange to conduct site monitoring visits remotely. Following each monitoring visit, the site monitor will prepare a site visit report and letter to the DSMB, the DCC regarding the findings, and the Study Principal Investigator. A representative from NCR will also attend the annual meetings of site directors and site coordinators and be available for teleconferences as needed.

15.0 Schedule and Milestones:

	STUDY MONTH																											
	1	2	3	4	5	6	7	8	9	10	11	12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36	37-39	40-42	43-45	46-48	post-study 1-12 mo.			
Finalize subcontracts	X	X																										
Finalize protocol and manual of operations with input from clinical sites	X	X																										
Begin monthly Steering Committee teleconferences	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Annual Steering committee meeting						X										X				X	X	X	X	X	X	X		
Begin monthly Coordinator teleconferences			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Annual Coordinator meeting						X										X				X				X				
Finalize DSMP including DSMB membership		X																										
Collect institutional cooling and proning protocols		X																										
Finalize management/communication plan		X																										
Steering committee approval of final protocols				X																								
Submit protocol for HRPO approval		X																										
Submit protocol for central (Western) IRB approval		X																										
Submit protocol for Brooke Army MC IRB approval		X																										
Central IRB approval all sites except BAMC	X																											
Finalize data collection and management plan with CSPCC, clinical sites, DCC	X	X																										
Finalize electronic CRFs with CSPCC		X	X																									
Finalize data completeness and quality monitoring reporting plan		X	X																									
Finalize site performance plan		X	X																									
Finalize comprehensive lab plan (clinical lab certifications, payment plan for research lab tests, plan for shipping, storage, inventory of samples for UM Cytokine Core Lab)		X	X																									
Complete on-line GCP/human research protection training			X																									
On-line training for randomization and electronic data capture (CSPCC)		X	X																									
Anticipated approvals by HRPO and IRBs				X																								
Submit final approved protocol to DSMB				X																								
Semi-annual DSMB teleconferences					X							X		X		X		X		X		X		X		X		
Register with clinicaltrials.gov					X																							
Initiation site visits				X	X	X	X																					
Activation of sites for randomization					X	X	X																					
Write descriptive paper about CHILL trial										X	X	X																
Patient enrollment (8 per year per site)								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Time expected to reach 25% recruitment goal													X															
Time expected to reach 50% recruitment goal																X												
Time expected to reach 75% recruitment goal																			X									
Time expected to reach 100% recruitment goal																						X						
Semi-annual clinical monitor site visit (KAI)												X		X		X		X		X								
Site closeout																	X					X	X					
Collection of data related to study endpoints										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Database lock																							X					
Data analysis																								X	X			
Write main paper																												

Fig. 1 Schedule of CHILL Study Milestones

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